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☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) **$110.00**

Complete if Known	
Application Number	09/730,663
Filing Date	December 6, 2000
First Named Inventor	Hageman, M.J.
Examiner Name	G.M. Shameem
Group Art Unit	1626
Attorney Docket No.	C-3405/0/US

METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☒ Deposit Account:

Deposit Account Number: 19-1025

Deposit Account Name: Pharmacia Corporation

The Commissioner is authorized to: *(check all that apply)*

☐ Charge fee(s) indicated below ☐ Credit any overpayments

☒ Charge any additonal fee(s) during the pendency of this application

☐ Charge fee(s) indicated below, **except for the filing fee** to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	750	2001	375	Utility filing fee	
1002	330	2002	165	Design filing	
1003	520	2003	260	Plant filing fee	
1004	750	2004	375	Reissue filing	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($)

2. EXTRA CLAIM FEES FOR UTILITY AND

	Extra Claims			Fee from below	Fee Paid
Total Claims		-20** =	0	X =	0.00
Independent Claims		- 3** =	0	X =	0.00
Multiple Dependent				=	

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	84	2201	42	Independent claims in excess of 3
1203	280	2203	140	Multiple dependent claim, if not paid
1204	84	2204	42	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) **$0.00**

***or number previously paid, if greater; For Reissues, see above*

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non - English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	410	2252	205	Extension for reply within second month	
1253	930	2253	465	Extension for reply within third month	110.00
1254	1,450	2254	725	Extension for reply within fourth month	
1255	1,970	2255	985	Extension for reply within fifth month	
1401	320	2401	160	Notice of Appeal	
1402	320	2402	160	Filing a brief in support of an appeal	
1403	280	2403	140	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,300	2453	650	Petition to revive - unintentional	
1501	1,300	2501	650	Utility issue fee (or reissue)	
1502	470	2502	235	Design issue fee	
1503	630	2503	315	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR § 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Statement	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	750	2809	375	Filing a submission after final rejection (37 CFR § 1.129(a))	
1810	750	2810	375	For each additional invention to be examined (37 CFR § 1.129(b))	
1801	750	2801	375	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) _____

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) **$110.00**

SUBMITTED BY				Complete *(if applicable)*	
Name (Print/Type)	James C. Forbes	*Registration No. (Attorney/Agent)*	39,457	*Telephone*	847-581-6090
Signature	James C Forbes			*Date*	June 14, 2003

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C-3405/0/US

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1626

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Hageman, M.J. *et al.*	ATTORNEY DOCKET NO.:	C-3405/0/US
SERIAL NO.:	09/730,663	GROUP ART UNIT:	1626
FILED:	December 6, 2000	EXAMINER:	G.M. Shameem

TITLE: SOLID STATE FORM OF CELECOXIB HAVING ENHANCED BIOAVAILABILITY

DATE: July 14, 2003

CERTIFICATE OF MAILING

I hereby certify that this document and its listed enclosures are being deposited with the United States Postal Service as First Class Mail in an envelope addressed to:

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on (date) July 14, 2003. Susan B Gould

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

PETITION FOR EXTENSION OF TIME UNDER 37 C.F.R. § 1.136(a)

Applicant hereby requests an extension of time of one month in which to respond to the Office Action dated March 21, 2003 in the above identified Application. That Office Action set a shortened statutory period of three months for response. Please charge $110 or the fee required under 37 C.F.R. § 1.17(a)(1) to Deposit Account No. 19-1025.

RESPONSE TO OFFICE ACTION DATED JUNE 7, 2002

Claims 1 and 15 are pending in the above-identified Application and stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,466,823 (Talley).

The Examiner has maintained the rejection for reasons given in the Office Action of June 7, 2002 (Paper #11), indicating that Applicant's response of December 9, 2002 has been "fully considered but ... not deemed persuasive". Those reasons for rejection can be summarized as follows:

- "no patentable distinction" found by the Examiner, citing *In re Weijlard*, 69 USPQ 86 (CCPA 1946), in the concept of a chemical compound in crystalline form over the same compound in amorphous form (Paper #11, page 3, lines 6–8); and
- an assertion that "one skilled in the art would have been motivated to prepare ... amorphous forms of known pharmaceutically useful compounds with the expectation of obtaining a pharmaceutically useful benefit" (Paper #11, page 3, lines 19–21).

Applicant's rebuttal of the first of these arguments for rejection, set forth in the response of December 9, 2002, received no comment in the present Action, and it is therefore believed that the Examiner accepts Applicant's position that there is indeed a patentable distinction in the present case, wherein the inventors went against Talley's teaching of crystalline celecoxib to prepare amorphous celecoxib (as opposed to proceeding from amorphous to crystalline form, which was the fact situation in *In re Weijlard*).

The present rejection instead focuses on the second of the above arguments. Applicant respectfully submits (a) that the Examiner's assertion of motivation with expectation of success is incorrect; (b) that a *prima facie* case of obviousness has not been made; and (c) that the benefits of amorphous celecoxib as set forth in the present specification are sufficiently great and unexpected as to be evidence of nonobviousness even if such a *prima facie* case had been made.

1. Motivation to prepare amorphous celecoxib is not present in the art.

As support for the assertion of motivation, the Examiner cites pages 349–472 of Stavchansky & McGinity (1990) *Bioavailability in Tablet Technology*. Chapter 6 in *Pharmaceutical Dosage Forms: Tablets, Vol. 2,* ed. Lieberman *et al.*, pp. 349–569. New York: Marcel Dekker. This reference, hereinafter "Stavchansky", is accorded its correct bibliographic citation above for the record.

Stavchansky is cited in the present Action as teaching that "amorphous solids will, in general, be better absorbed than will crystalline ones". Office Action of March 21, 2003, page 2, lines 21–22. It may be true that a person of ordinary skill, reading this single sentence out of context, might at the time of the present invention have thought it a good idea to try to make amorphous celecoxib. However, it is respectfully submitted that the Examiner has improperly disregarded MPEP 2141.02, last paragraph, which requires that "A prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead

away from the claimed invention", citing *Gore v. Garlock*, 220 USPQ 303 (Fed. Cir. 1983). Emphasis in original.

When the relevant portion of Stavchansky (Section N at pages 462–465) is read as a whole as required by MPEP 2141.02, it is seen that amorphous forms of drugs can have undesirable effects that offset possible benefits of improved absorption. For instance, "the amorphous state is predictably unstable." Stavchansky, page 465, line 7. Examples cited include penicillin G sodium and potassium salts, and novobiocin. "Crystalline potassium penicillin can withstand dry heat for several hours without significant decomposition. Under similar conditions, the amorphous forms lose considerable activity." Stavchansky, page 465, lines 11–13. Stavchansky thus provides disclosure that teaches away from the present invention, and does not, when read as a whole, clearly motivate one of ordinary skill to try to modify Talley's celecoxib by preparing an amorphous form of the drug.

Stavchansky is also cited in the present Action as teaching that the "amorphous state reduce[s] the particle size of the drug and result[s] in a faster rate of dissolution than occurs with a crystalline form." Office Action of March 21, 2003, sentence bridging pages 2–3. It is respectfully pointed out that this is a misquotation; Stavchansky actually states that "Techniques commonly used in preparing drugs in the amorphous state generally reduce the particle size of the drug ...". Stavchansky, page 465, lines 4–6, emphasis added. In this regard, it is noted that the claims presently in consideration are not restricted to amorphous celecoxib prepared by any particular technique, nor to any particular particle size range of celecoxib. It is further noted that Stavchansky teaches "reduction in particle size is not desirable in all cases" and cites nitrofurantoin as an example wherein smaller particles increase gastrointestinal irritation, "which explains why a macrocrystalline rather than an amorphous form of nitrofurantoin appears in the marketed product." Stavchansky, page 454, lines 20–25.

Further, an impermissible "obvious to try" standard has been applied by the Examiner. Stavchansky teaches that "the formulation of a stable and bioavailable product requires a thorough study of the physicochemical properties of drug and tablet to ensure efficacy." Stavchansky, page 393, lines 21–23. Moreover, as also taught by Stavchansky, there are a multitude of potential approaches to improving bioavailability, including those involving particle size (page 453), prodrugs (page 458), dispersants (page 459), crystalline forms (page 462), solvates and hydrates (page 465), complexation (page 467), excipients (page 472) and surface-active agents (page 476).

Theoretical considerations and general observations as presented by Stavchansky may

suggest possible utility of an amorphous compound, and the Examiner appears to have concluded that one of ordinary skill in the art would have found it obvious to try to make amorphous celecoxib. However, the "obvious to try" standard is impermissible.

> "The admonition that 'obvious to try' is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. ... In others, what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it."

In re O'Farrell, 7 USPQ2d 1673 (Fed. Cir. 1988); MPEP 2145.X.*B.*

Stavchansky teaches numerous possible choices to make a more bioavailable compound with only general guidance as to how to achieve it. The amorphous state is but one of a multitude of choices in Stavchansky. At best, this constitutes an "obvious to try" rationale.

Thus no suggestion or motivation to modify Talley's crystalline celecoxib to make amorphous celecoxib is found in Talley, nor does Stavchansky provide the necessary motivation when read as a whole. Absent such motivation, a *prima facie* case of obviousness cannot be sustained. MPEP 2143.

2. There was no reasonable expectation of success at the time the invention was made.

Even if, *arguendo*, there was an expectation of superior absorption based on a reading of Stavchansky, there was no reasonable expectation at the time the present invention was made that amorphous celecoxib could be made. Stavchansky does not teach that amorphous drugs can be made, merely that if amorphous drugs can be made one might predict superior absorption.

Reasonable expectation of success requires "at least some degree of predictability". MPEP 2143.02, second subsection. In its previous response, Applicant submitted "It was not even predictable that an amorphous form of celecoxib could exist or be made." Response of December 9, 2002, page 2, lines 24–25. Although Applicant supported this statement with evidence from Remington (1995), *The Science and Practice of Pharmacy,* 19th ed., page 168, the Examiner dismisses the statement as "speculation on Applicant's behalf because one of ordinary skill in the art [is] deemed to be aware of all the pertinent art in the field." Office

Action of March 21, 2003, page 2, lines 19–21.

Remington was cited by Applicant as teaching: "Certain materials are easy to cast into a glassy [*i.e.*, amorphous] state, others can be made glassy with some difficulty and, some, seemingly not at all. At present there seems to be no specific theory to help predict this behavior." Response of December 9, 2002, page 2, lines 25–27. Thus Applicant's statement that it was not predictable that amorphous celecoxib could exist or be made is emphatically not speculation but is a statement of fact supported by one of the most reputable handbooks of pharmaceutical science. The Examiner has not challenged Remington's teaching, nor has he cited another reference with contrary teaching. Mere dismissal as "speculation" of the evidence of unpredictability adduced by Applicant is insufficient to overcome that evidence. The appended clause "because one of ordinary skill in the art [is] deemed to be aware of all the pertinent art in the field" carries no weight since the Examiner has cited no pertinent reference against Remington's teaching of unpredictability. The only reference cited in this context by the Examiner, namely Stavchansky, has nothing to say on the question of predictability with which an amorphous compound can be made, only, as pointed out above, the question of expectation of a benefit in absorption if the amorphous form exists.

Thus, in view of the unchallenged lack of predictability that amorphous celecoxib could exist or be made, Applicant has shown that at the time the present invention was made there was no reasonable expectation of success. Absent such reasonable expectation of success, a *prima facie* case of obviousness cannot be sustained. MPEP 2143.

3. The present invention represents no "mere change in form".

The Examiner suggests that one skilled in the art would have had a "reasonable expectation" that changing the form or state of a compound would result in "compounds of similar activity". Office Action of March 21, 2003, page 3, lines 2–5, emphasis added. Thus the Examiner himself appears to discount Stavchansky's teaching of differences in absorption between amorphous and crystalline forms of a drug, in order to suggest that the expectation of the present invention is that it constitutes no more than a "mere change of form" unaccompanied by advantages stemming from the new form. As quoted by the Examiner, "Mere change of form in and of itself does not disclose novelty." *Ex parte Conn & Norman*, 119 USPQ 388, 1956.

Applicant respectfully draws the Examiner's attention to its previous response, wherein the quotation from *Ex parte Conn & Norman* is shown to derive from *Union Carbide*

v. American Carbide, 181 F 104. Response of December 9, 2002, page 3, lines 7–20. In both *Union Carbide* and *Ex parte Conn & Norman* the fact situations were found to support patentable novelty, as it was determined in each case that the change of form was accompanied by advantages stemming from the new form. A similar fact situation is found in the present application, thus amorphous celecoxib does not represent a "mere change of form".

Specifically, the Examiner's attention is once again respectfully drawn to the present specification at page 31, Table 3.

In a pharmacokinetic study in dogs, a tablet comprising amorphous celecoxib of the invention exhibited an approximately twofold higher C_{max} and an approximately twofold higher AUC, *i.e.*, a doubling of bioavailability, by comparison with a prior art capsule comprising crystalline celecoxib. Furthermore, a blood plasma celecoxib level of 1011 ng/ml, reached in 1.2 hours with the prior art crystalline form, was reached in just 0.5 hour, *i.e.*, less than half the time, with the amorphous form of the invention.

According to the present Action, unless unobvious and unexpected results can be shown, the rejection must be maintained. Office Action of March 21, 2003, page 3, lines 6–7. Applicant respectfully submits that the data shown in Table 3 of the specification constitute the unobvious and unexpected results necessary to overcome the present rejection, even if a *prima facie* case of obviousness existed (which is not admitted herein). These data clearly show that amorphous celecoxib is not a "mere change in form", rather it is a novel and unobvious material having significant benefit over prior art crystalline celecoxib.

"Because the advantages afforded by the claimed compound stem from its new form, [and] since the compound is neither taught nor suggested by the prior art, its novelty coupled with the unobvious results thereby renders it patentable." *Ex parte Conn & Norman.* A similar fact situation presents itself here; accordingly the present claims are believed allowable.

4. Conclusion

For the reasons set forth above, Applicant respectfully traverses the present rejection under 35 U.S.C. § 103(a) and submits that the claims presently in consideration are in condition for allowance.

Respectfully submitted,

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Enclosure:
Fee Transmittal Sheet